Notice of Allowability	Application No.	Applicant(s)	
	10/089,380	SAITO ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the Paper filed 2 August 2005*.

2. ☒ The allowed claim(s) is/are *1,3-10,13-17,22 and 25-30*.

3. ☒ The drawings filed on *29 March 2002* are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

5-10-05

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Craig McRobbie on 18 August 2005.

The application has been amended as follows:

In the specification:

Replace the Abstract with the following:

ABSTRACT

To provide DNA comprising mutant FRT sequence which causes recombination reaction between two mutant FRT sequences having an identical sequence to each other but does not cause recombination reaction with a wild-type FRT sequence, in the presence of FLP recombinase; and a method for performing high-efficiency, gene insertion or gene replacement. A DNA comprising a mutant FRT sequence ~~(any one of SEQ ID NOs: 2 to 5)~~. A DNA comprising a mutant FRT sequence possessing (A) causing no specific DNA recombination reaction with wild type FRT, even if FLP recombinase is present, and (B) causing specific DNA recombination reaction with another mutant FRT sequence having an identical sequence thereto in the presence of recombinase FLP~~, wherein the mutant FRT sequence has substitutions of at~~

~~least one nucleotide in a region other than the spacer region in the sequence, a cell which is transformed with the DNA~~; gene replacement method using the DNA in the presence of recombinase FLP; ~~a transgenic animal carrying the DNA in a chromosome; a pharmaceutical comprising the DNA;~~ and a specific DNA recombination method, characterized in that a specific DNA recombination reaction is carried out by using two mutant FRT sequences ~~(SEQ ID NO: 32)~~ in the presence of recombinase FLP.

Replace the paragraph beginning on page 4, line 14 with the following:

--Concretely, the present invention relates to:

[1] A DNA comprising a mutant FRT sequence having a sequence resulting from substitution of nucleotides at middle 8-bp (spacer region) in the following wild type FRT sequence (SEQ ID NO: 1) derived from yeast 2 μ DNA:

	12 34 56 78	
5'-GAAGTTCCTATAC	TTTCTAGA	GAATAGGAACTTC-3'
	spacer region	

with nucleotide sequences selected from the group consisting of the following (1) to (4):

(1) TCTCTGGA (f2161)(nucleotides 14-21 of SEQ ID NO:2)

(2) TCTCCAGA (f2151)(nucleotides 14-21 of SEQ ID NO:3)

(3) TATCTTGA (f2262)(nucleotides 14-21 of SEQ ID NO:4) and

(4) TTTCTGGA (f61)(nucleotides 14-21 of SEQ ID NO:5)

wherein said mutant FRT sequence is any one of SEQ ID NOS: 2 to 5;--

Replace the paragraph beginning on page 9, line 19, with the following:

--The DNA comprising the mutant FRT sequence of the present invention is a DNA comprising a mutant FRT sequence having a sequence resulting from substitution of nucleotides at middle 8-bp (spacer region) in the following FRT sequence (SEQ ID NO: 1) derived from yeast 2 μ DNA:

	12 34 56 78	
5'-GAAGTTCCTATAC	TTTCTAGA	GAATAGGAACTTC-3'
	spacer region	

with nucleotide sequences selected from the group consisting of the following (1) to (4):

(1) TCTCTGGA (f2161)(nucleotides 14-21 of SEQ ID NO:2)

(2) TCTCCAGA (f2151)(nucleotides 14-21 of SEQ ID NO:3)

(3) TATCTTGA (f2262)(nucleotides 14-21 of SEQ ID NO:4) and

(4) TTTCTGGA (f61)(nucleotides 14-21 of SEQ ID NO:5)

wherein said mutant FRT sequence is any one of SEQ ID NOs:2 to 5. Since the DNA of the present invention comprises a sequence selected from the group consisting of the items (1) to (4) mentioned above, there are exhibited excellent properties such that in the presence of FLP recombinase, a recombination reaction between two mutant FRT sequences each having an identical sequence to each other is caused, but no recombination reaction with the wild-type FRT sequence is caused. Further, by using the DNA of the present invention, gene replacement can be performed with an even higher efficiency of gene replacement.--

In the claims

It is noted that the claim set filed 2 August 2005 identifies claim 17 as "Currently Amended". The proper status of the claim is "Previously presented", as there have been no changes made relative to the claim set filed 8 December 2004.

Claims 2, 11, 12, 21, 23 and 24 are canceled.

The claims are amended as follows:

1. (Currently amended) An isolated DNA encoding a mutant FRT sequence ~~derived from yeast 2μ DNA~~ comprising ~~a~~ the nucleotide sequence shown in ~~SEQ ID NO:1, wherein the nucleotides of the middle 8 bp spacer region are replaced with~~ any one of SEQ ID NOS: 2 to 5.

3. (Currently amended) The isolated DNA according to claim 1 ~~or 2~~, wherein said mutant FRT sequence possesses ~~the~~ a property of causing no specific DNA recombination reaction with a second ~~mutant~~ FRT sequence having a different sequence in the 8-bp spacer region in the presence of recombinase FLP.

4. (Currently amended) An isolated DNA comprising at least one wild type FRT sequence comprising SEQ ID NO: 1 and at least one mutant FRT sequence ~~defined in~~ of claim 1.

5. (Currently amended) The isolated DNA according to claim 4, having a desired nucleotide sequence between the wild type FRT sequence and the mutant FRT sequence.

6. (Currently amended) An isolated DNA comprising at least two mutant FRT sequences ~~defined in~~ of claim 3, wherein the at least two mutant FRT sequences are different relative to one another in the 8-bp spacer region.

7. (Currently amended) The isolated DNA according to claim 6, further comprising a desired nucleotide sequence between ~~the~~ two of the at least two mutant FRT sequences.

8. (Currently amended) An isolated or cultured cell which is transformed with the DNA of claim 4 *in vitro*.

9. (Currently Amended) A method for replacing a nucleotide sequence *in vitro*, comprising the steps of

reacting a first DNA comprising in sequential order a wild type FRT sequence comprising SEQ ID NO: 1, a first nucleotide sequence of interest and a mutant FRT sequence ~~shown in~~comprising any one of SEQ ID NOS: 2-5 with a second DNA comprising in sequential order a wild type FRT sequence comprising SEQ ID NO: 1, a second nucleotide sequence of interest which nucleotide sequence is different from that of the first nucleotide sequence of interest, and a mutant FRT sequence which is identical to the mutant FRT sequence of the first DNA in the presence of recombinase FLP,

thereby obtaining a DNA in which the first nucleotide sequence of interest is replaced by the second nucleotide sequence of interest in the first DNA.

10. (Currently amended) A method for replacing a nucleotide sequence *in vitro*, comprising the steps of

reacting a first DNA comprising in sequential order a mutant FRT sequence ~~defined in~~of claim 3, a first nucleotide sequence of interest and a second mutant FRT sequence of claim 3, wherein the first and second mutant FRT sequences are different relative to one another in the 8-bp spacer region with a second DNA comprising in sequential order the first mutant FRT sequence, a second nucleotide sequence of interest which nucleotide sequence is different from that of the first nucleotide sequence of interest, and the second mutant FRT sequence in the presence of recombinase FLP,

thereby obtaining a DNA in which the first nucleotide sequence of interest is replaced by the second nucleotide sequence of interest in the first DNA.

13. (Currently amended) The method according to claim 9 ~~or 21~~, wherein said first DNA is a chromosomal DNA of a cell, and said second DNA is a plasmid DNA or a DNA of double-stranded circular DNA virus.

14. (Currently amended) The method according to claim 9 ~~or 21~~, wherein said first DNA is a chromosomal DNA of a cell~~, and said second DNA has a property for forming a double-stranded circular DNA by intracellular conversion~~.

15. (Currently amended) The method according to claim 9 ~~or 21~~, wherein said first DNA is a chromosomal DNA of a double-stranded DNA virus, and said second DNA is a plasmid DNA or a DNA of a double-stranded circular DNA virus.

16. (Currently Amended) The method according to claim 9 ~~or 21~~, wherein said first DNA is a chromosomal DNA of a double-stranded DNA virus~~, and said second DNA has a property of forming a double-stranded circular DNA by intracellular conversion~~.

25. (Currently amended) The method according to claim 10, wherein said first DNA is a chromosomal DNA of a cell, and said second DNA is a plasmid DNA or a DNA of a double-stranded circular DNA virus.

26. (Currently amended) The method according to claim 10, wherein said first DNA is a chromosomal DNA of a cell~~, and said second DNA has a property for forming a double-stranded circular DNA by intracellular conversion~~.

27. (Currently amended) The method according to claim 10, wherein said first DNA is a chromosomal DNA of a double-stranded DNA virus, and said second DNA is a plasmid DNA or a DNA of a double-stranded circular DNA virus.

28. (Currently amended) The method according to claim 10, wherein said first DNA is a chromosomal DNA of a double-stranded DNA virus~~, and said second DNA has a property of forming a double-stranded circular DNA by intracellular conversion~~.

The following is an examiner's statement of reasons for allowance:

The amendments filed 2 August 2005 overcome all of the outstanding rejections.

The new matter rejection set forth beginning on page 8 of the previous Office Action, mailed 2 March 2005, is **withdrawn**. A review of the sequence listing filed in the application reveals that the sequences set forth as SEQ ID NO: 2-5 comprise the entire 34-bp sequence of the claimed mutant FRT sequences. References to SEQ ID NO: 2-5 in the specification and claims are amended such that they are consistent with the sequences as set forth in the sequence listing.

Rejoinder of non-elected sequences

The restriction requirement between SEQ ID NO: 2-5 is hereby **withdrawn**.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636